Journal of Dermatological Treatment (2004) 15, 295–302
 ISSN 0954-6634
DOI: 10.1080/09546630410033808

A topical azithromycin preparation for the treatment of acne vulgaris and rosacea

RC McHugh, A Rice, ND Sangha, MA McCarty, R Utterback, JM Rohrback, BE Osborne, AB Fleischer Jr and SR Feldman

Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

BACKGROUND: Erythromycin is a common therapy for acne and rosacea. A newer macrolide, azithromycin, offers superior tissue distribution and cellular concentration and is an effective oral anti-acne agent. Topical formulations such as erythromycin have been a major clinical therapy for acne. To date, no topical solution of azithromycin is available for the treatment of acne.

OBJECTIVE: To prepare a stable topical 2% azithromycin formulation that could be used in an acne clinical trial to determine the efficacy of topical azithromycin in treating subjects with acne vulgaris and acne rosacea.

METHODS: The study was divided into two phases. In phase I, azithromycin was prepared over a range of ethanol/water concentrations to determine solubility. The stability of a 2% azithromycin in 60% ethanol/water preparation was assessed by high-pressure liquid chromatography. The temperature, light, and pH dependence of the stability was also assessed. In phase II, a single center, randomized, double-blind, treatment-controlled study compared once-nightly application of topical 2% azithromycin versus 2% erythromycin. A total of 20 subjects with moderate inflammatory acne and 20 with rosacea were examined clinically at 0, 2, 4, 8, and 12 weeks for a 12-week period. Efficacy was evaluated with the Physician's Visual Analog Scale evaluation (PVAS), the papulopustule count, and acne severity rating (in subjects with acne).

RESULTS: In phase I, azithromycin was soluble in 60% ethanol/water. A 2% azithromycin in 60% ethanol/water solution maintained stability at room temperature for up to 26 weeks but at 37°C there was some decay (16%) at 26 weeks. The stability was greatest at pH 6.8 and was unaffected by ambient light exposure. In phase II, the number of inflammatory lesions decreased in both acne and rosacea subjects treated with 2% erythromycin (7.56, $p=0.03$ and 4.4, $p=0.01$, respectively). Azithromycin was not as effective for the treatment of rosacea. Both azithromycin ($p=0.01$) and erythromycin ($p=0.03$) treatment significantly reduced the inflammatory lesion count in acne vulgaris. No significant adverse events were identified in the acne group. In patients with rosacea, transient irritation occurred in five patients.

CONCLUSIONS: A 2% azithromycin in 60% ethanol/water solution can be prepared and is stable for at least 6 months at room temperature. The methodology and power of the study were adequate to identify improvement in acne vulgaris and rosacea. Though it appears the formulation of topical azithromycin was at least comparable with topical erythromycin, larger studies would be needed to determine whether topical azithromycin has any significant advantage over topical erythromycin. (*J Dermatol Treat* (2004) **15**: 295–302)

Correspondence:
Steven R Feldman, MD, PhD. Wake Forest University School of Medicine, Department of Dermatology, Winston-Salem, NC 27157, USA. Tel +1 336 716 7740; Fax +1 336 716

Received 4th March 2003
Accepted 6th April 2004

Keywords: Acne vulgaris — Azithromycin — Erythromycin — Randomized trial — Rosacea — Topical antibiotics

Introduction

Acne vulgaris is the most common disease seen by a dermatologist, affecting about 85% of adolescents in some form.[1] The disease mechanism is attributed to hyperkeratotic follicular plugging and sebum accumulation, bacterial breakdown of sebum, and release of inflammatory mediators such as free fatty acids (FFA).[2] Rosacea is also a disorder affecting the pilosebaceous units, and patients are generally older (>30 years of age) and have associated symptoms of facial flushing and telangiectasias.[3] Lesions are typically papules and pustules with a centrofacial distribution. Non-inflammatory comedones are not present in rosacea.[4]

Disease management for acne is directed at the type of clinical lesions. Non-inflammatory acne lesions and severe acne respond best to retinoids.[2,5] Antibiotics are an important component of treatment for inflammatory acne and rosacea. Oral antibiotics are effective for both these conditions, but have the potential for significant side effects.[6] Topical antibiotics have the advantages of reduced risk of systemic side effects, reduced resistance by enteric bacteria, and an overall reduced drug amount. In contrast to systemic medication, the complications of topical antibiotics such as skin irritation and erythema are generally minor. Rarely is there significant systemic absorption.[7] Generally, topical antibiotics are clinically effective in mild to moderate acne and are less effective against severe acne and non-inflamed lesions.

Topical erythromycin is a macrolide antibiotic that has been shown in many studies to be an effective and safe therapeutic first-line agent for acne vulgaris.[8–10] It is also considered an efficacious topical alternative to oral tetracyclines given for the treatment of acne rosacea.[11] Topical application of a 2% erythromycin is effective, resulting in a decrease of inflammatory lesions after 2 weeks of therapy, as well as a reduction of comedones in 2 months.[7] For acne vulgaris, the anti-inflammatory effect is thought to be secondary to inhibition of *Propionibacterium acnes* and the subsequent decrease in free fatty acid production, not entirely a direct bacteriocidal effect. The reason for response in acne rosacea patients is unclear but may be in part by a similar mechanism.

Azithromycin is a semi-synthetic macrolide antibiotic active against common *Staphylococcal* species, *P. acnes*, as well as other common aerobic and anaerobic organisms. Oral use is indicated for the treatment of skin and skin structure infections, upper and lower respiratory tract infections, urethritis and cervicitis. Azithromycin has a longer half-life (68 hours) than other class members when taken orally. This extensive half-life is due in part to the ability to move rapidly from blood to tissues where it remains for prolonged periods.[12] Oral azithromycin is as effective as oral erythromycin in the treatment of acne but is more convenient due to its less frequent dosing.[12]

Oral antibiotics have the potential for significant side effects. Common complaints include gastrointestinal upset, headaches, and candidiasis. More serious, and at times fatal, occurrences can include blood dyscrasias and anaphylactic shock.[13] Topical antibiotics have the advantages of reduced risk of systemic side effects, reduced resistance by enteric bacteria, and overall less drug amount. In contrast to systemic medication, the complications of topical antibiotics such as skin irritation and erythema are generally minor. Rarely is there significant systemic absorption.[13]

Topical antibiotics are often prepared in solution vehicles, often using alcohol to improve penetration. Alcohol-based solutions are most appropriate for patients with oily skin.[8] The pharmacokinetic profile of azithromycin – extensive tissue distribution, high concentrations taken up by white blood cells and fibroblasts, and long half-life – suggests the potential for greater efficacy compared with erythromycin for topical treatment of acne. To date, no topical solution of azithromycin has been made available for the treatment of acne. The purpose of this study was to prepare a stable topical 2% azithromycin formulation that could be used in an acne clinical trial to evaluate the efficacy of 2% topical azithromycin solution in the clearing of acne vulgaris and rosacea when compared with 2% topical erythromycin.

Methods

Phase I was divided into two parts: (1) azithromycin solubility in various ethanol/water concentrations; (2) the stability of 2% azithromycin in 60% ethanol/water was determined. Phase II consisted of a single center, randomized, double-blind, parallel controlled treatment study performed in subjects with moderate inflammatory acne and rosacea.

Phase I

Materials

A commercial preparation of lyophilized azithromycin (Zithromax for IV infusion; Pfizer, New York, NY, USA) was used to prepare test formulations. Other reagents were obtained from Sigma (St Louis, MO, USA) unless otherwise specified.

Solubility

Intravenous azithromycin 500 mg vials were dissolved with ethanol/dH_2O concentrations of 100%, 90%, 80%, 70%, and 60%. After adding an appropriate volume of dH_2O to the azithromycin vials, contents were vigorously vortexed for 5 minutes. The appropriate volume of ethanol was added and vortexed for 2 further minutes. The 500 mg vials of azithromycin were diluted to a final volume of 25 ml to yield a 20 mg/ml (2%) azithromycin solution. Vehicle formulations were then allowed to sit overnight at room temperature. Observations regarding precipitate and crystallization were noted on the following day. As discussed below, a 2% azithromycin in 60% ethanol/water formulation was used in further analyses.

Stability

The stability of the 2% azithromycin in 60% ethanol/water formulation was evaluated by using a high-performance liquid chromatography (HPLC) assay. Standard curves were established for each experimental run. All concentration levels during the study were measured with an HPLC assay based on a previously published method, with noted exceptions.[9] The HPLC system consisted of a Waters 600 pump and control module, a Waters 717+ autosampler, Alltech Associates Model CH 1445 column heater, Waters Millennium software and a Spectra-system UV 2000 UV/Vis detector. The analytical column employed was a Hamilton PRP-1 5 µm, 150 × 4.6 mm. The mobile phase consisted of 10% (v/v) 20 mM Tris, 20% (v/v) 20 mM tetrabutyl ammonium hydroxide, 10% (v/V) isopropanol, and 60% (v/v) acetonitrile. Azithromycin was detected at 214 nm, range=0.2 AUFS, and the column heater was set at 50°C. Standard solutions were prepared from a 100 mg/ml azithromycin in water stock solution aliquotted and stored at −80°C. On the day of analysis the stock solution was diluted 1:10 with dH_2O to prepare a 10 mg/ml solution. This 10 mg/ml stock solution was diluted to 2.0 mg/ml, 1.0 mg/ml, 0.5 mg/ml, 0.25 mg/ml, and 0.125 mg/ml to establish a standard curve for azithromycin concentration (Figure 1).

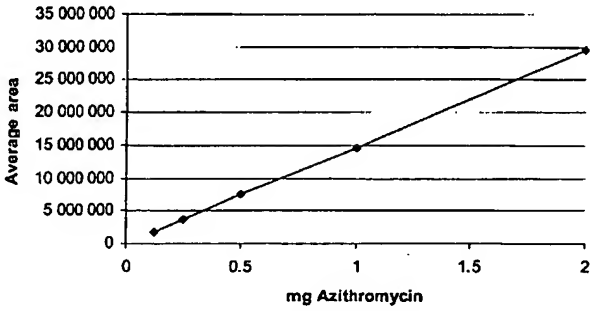

Figure 1
HPLC standard curve measuring azithromycin concentrations (dH_2O standard solution, mg/ml).

Stability was assessed over a 6-month test period. Azithromycin concentrations were measured by HPLC at 0, 1, 2, 4, 8, 12, and 26 weeks. Variable conditions included storage at room temperature (RT) in the dark or light, and at 37°C in the dark. The 20 mg/ml azithromycin stock solution was diluted 1:19 with dH_2O to produce 1 mg/ml concentrations in 300 µl aliquots. Three replicates were prepared for each condition. Each replicate was measured twice at the specified events (1, 2, 4, 8, 12, and 26 weeks). The mean of these two measurements was reported as the aliquot's concentration value, and the mean and standard deviation of the three replicate means are reported. A parallel standard with fresh azithromycin in dH_2O was tested using similar methodology. When and if the concentration fell below 80% of the original concentration (16 mg/ml), the remaining time points were discontinued.

The effect of pH on drug stability was established with a 6-month study. Azithromycin solutions were prepared from 500 mg vials of azithromycin with 25 ml 60% ethanol added to produce 20 mg/ml stock solution. The stock solutions were diluted 1:19 with dH_2O to produce a concentration of 1 mg/ml in 300 µl. The pH was adjusted to 6.3, 6.8, 7.3, and 7.8 with two aliquots per pH measurement. At 0, 8, and 26 weeks, quantitative assessment of azithromycin concentrations were measured as described above.

Phase II

A randomized, double blind, parallel controlled treatment study was performed in subjects with moderate inflammatory acne and rosacea. The Institutional Review Board of the Wake Forest University School of Medicine approved this single center study. Twenty subjects with acne and 20 subjects with rosacea met the inclusion criteria (described below). Participants were assigned sequential numbers and were then randomized into blocks of 10 to apply either 2% azithromycin (in 60% ethanol/40% water solution) or a commercial

preparation of 2% erythromycin solution (obtained from the North Carolina Baptist Hospital pharmacy).

Subjects were to apply their assigned drug once daily in the evenings for a period of 12 weeks. Each subject was instructed to wash his or her face before application of the study medication and to otherwise maintain his or her routine hygiene schedule. During the study, subjects used the same soap or facial cleanser and shampoo that they were using at baseline unless prohibited by the protocol.

Safety was assessed by reports of adverse drug reactions. Safety and efficacy parameters were evaluated at baseline and 12 weeks. Adverse events were also recorded at 4 and 8 weeks. Photographs were taken at regular intervals to evaluate the progress of the treatment. Efficacy was evaluated with the Physician's Visual Analog Scale evaluation (PVAS), the papulopustule count, and acne severity rating (for acne vulgaris only). One investigator recorded the overall severity using the PVAS evaluation as a modified visual analog scale. The following descriptors were used on the scale: worse (−1), no change (0), slightly better (+1), moderately better (+2), much better (+3), and completely clear (+4). The acne severity rating is based on the Allen and Smith Modified Grading scale: Grades 0, 2, 4, 6, and 8 are assigned and scores 1, 3, 5, and 7 can be used for intermediate conditions. 0=facial skin is clear; 2=about one-quarter of the facial area is involved with small papules (6–12) and comedones; 4=about half the facial area is involved with small papules and large or small comedones (a few pustules or large papules are usually present); 6=about three-quarters of the facial area is involved with papules and large open comedones (numerous pustules are usually present, some of which may be large); 8=practically all the facial area is involved with lesions (large prominent pustules are usually visible; lesions are usually highly inflammatory). Other types of acne (such as nodular or cystic) may be present.

Inclusion criteria

Eligible patients for this study were men or women aged 12–40 years with acne vulgaris, and men or women 30 years or older with acne rosacea. Women of childbearing potential agreed to use effective contraception for the duration of the study. Of those patients presenting with acne vulgaris, only those with moderately inflammatory acne, as defined by the presence of at least 15 inflammatory acne lesions and an acne severity rating of at least 3 but less than 8, were included in the study. Subjects with moderately severe acne rosacea, as defined by the presence of at least four inflammatory lesions, were included.

Subjects were in good general health, without evidence of acute or chronic diseases. Those selected were willing and able to apply study medication as directed, comply with study instructions and commit to all follow-up visits for the duration of the study. All subjects signed informed consent; a parent/legal guardian signature was required in the case of a minor.

Exclusion criteria

Women who were pregnant or lactating were excluded. Subjects with more than three nodulocystic lesions as well as those with other significant facial dermatoses, which could interfere with treatment or efficacy assessment, were also excluded. Subjects who had had a history of allergic reactions to the study drugs or the vehicle formulation were excluded. Subjects using the following medications within the restricted amount of time period were excluded from participation:

- non-steroidal anti-inflammatory drugs within 48 hours prior to the study
- oral contraceptives: current usage of less than 3 months (if current usage has been greater than 3 months, the dose must remain unchanged prior to and during the study)
- treatment with other topical anti-acne medications within the past 2 weeks
- treatment with oral anti-acne medications (other than Accutane) within the past month
- treatment with Accutane within the last 2 years
- treatment with theophylline, coumadin, zidovudine, digoxin, ergotamine, triazolam, carbamazepine, cyclosporine, hexobarbital and phenytoin within the past week.

Statistics

Statistical analyses were performed using SAS System software.

Results

Phase I

Solubility

After mixing and overnight saturation, azithromycin with 60% ethanol produced no visible precipitate or crystallization. Crystallization and/or precipitation were noted with ethanol solutions of 100%, 90%, 80%, and 70%. Subsequent additions of propylene glycol and HCl helped reduce precipitate and crystallization effects at ethanol concentrations greater than 60% (data not shown) but were not used in stability studies.

Stability

Stability data were obtained for 20 mg/ml (2%) azithromycin in both water (Figure 2) and in 60%

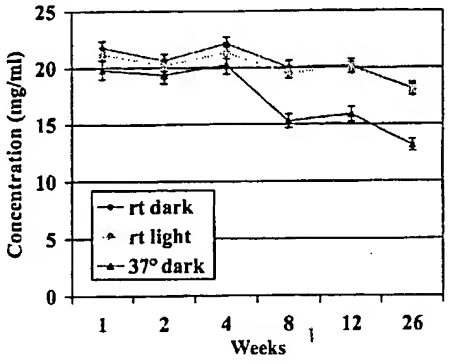

Figure 2
Twenty-six-week stability tests of 2% azithromycin in dH_2O. (rt=room temperature.)

ethanol (Figures 3 and 4). The mean of the three replicates of each condition are shown (RT dark, RT light, 37°C dark). Only minimal reductions in the concentration of 2% azithromycin in water were observed with up to 26 weeks of incubation at RT in either dark or light conditions (Figure 2). Decay was greater at 37°C (Figure 2). Stability was similar, though slightly greater, for the 2% azithromycin prepared in 60% ethanol (Figure 3). At room temperature, the 2% azithromycin/60% ethanol/pH 6.8 solution was essentially 100% stable over 8 weeks (1% reduction) with some decay at 26 weeks (4% reduction; Figure 4). These results were highly reproducible with standard deviations in the range of 0.0004 to 0.04 (Figure 4).

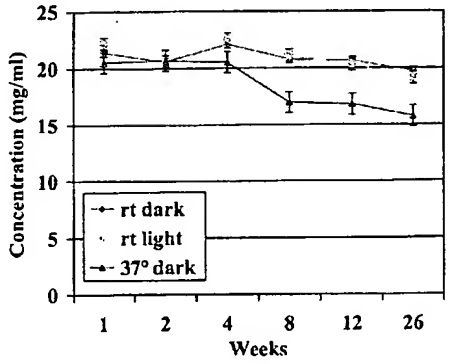

Figure 3
Stability of 2% azithromycin in 60% ethanol. (rt=room temperature.)

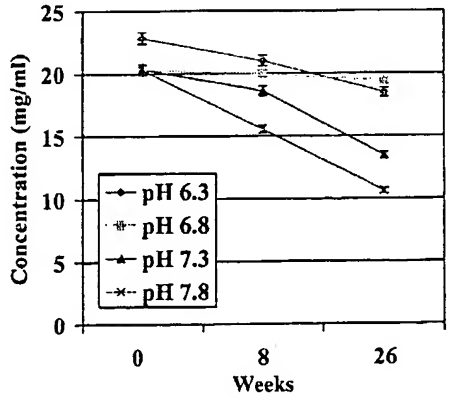

Figure 4
Dependence on pH of the stability of 2% azithromycin in 60% ethanol.

Phase II

Demographics

Of 40 enrolled subjects, 34 were women and 6 were men. Two subjects withdrew from the study prior to completion, and their data are not included in the analyses. Both subjects (one acne vulgaris participant and one acne rosacea participant) stopped taking their medications and were eventually lost to follow-up. The mean age of the 38 subjects was 33.9 (95% CI: 29.3, 38.6). Nineteen subjects with acne vulgaris had a mean age of 24.2 (95% CI: 20.6, 27.8), with 15 females and four males. Nineteen subjects with rosacea had a mean age of 44.8 (95% CI: 39.0, 50.6), with 18 females and one male. There was no significant difference in the initial severity of acne vulgaris patients ($p=0.3$) or rosacea patients ($p=0.2$) prior to randomization.

Acne vulgaris efficacy

Lesion measures (papulopustules, comedones, nodules, total lesions) and the PVAS were compared across treatments (Table I). These data are expressed as differences from initial mean lesion counts or PVAS score. Erythromycin treatment ($n=9$) showed a significant reduction in papules (five, $p=0.01$). However, azithromycin ($n=10$) treated subjects did not have significant reductions for any non-inflammatory lesions (p-values ≥ 0.08). Both azithromycin ($p=0.01$) and erythromycin ($p=0.03$) treatment significantly reduced the inflammatory lesion count.

Rosacea efficacy

For rosacea, neither lesion counts nor the PVAS score were significantly reduced by azithromycin treatment ($p \geq 0.4$; Table II). In contrast, subjects treated with erythromycin ($n=10$) showed a significantly greater reduction in papule count ($p=0.03$), total lesions ($p=0.03$), and PVAS score ($p=0.04$). Reductions in pustules, comedones, and nodules were not significantly different from their initial mean values (p-values $>$ 0.05). The erythromycin-treated group had a significant reduction in inflammatory lesions (4.4, $p=0.01$). There

	Lesion reductions in acne vulgaris after treatment with azithromycin or erythromycin			
	Azithromycin (n=10)		Erythromycin (n=9)	
Lesions assessed	Mean (95% CI)	p	Mean (95% CI)	p
Papules	3.0 (5.0, 11)	0.4	5.0 (1.4, 8.6)	0.01
Pustules	6.0 (−1.1, 13)	0.08	2.6 (−2.3, 7.4)	0.3
Comedones	2.3 (−5.9, 10)	0.5	13 (−6.5, 32)	0.2
Nodules	0.1 (−0.3, 0.5)	0.6	0.22 (−0.3, 0.7)	0.4
Total lesions	11 (−1.2, 24)	0.07	20 (−1.3, 41)	0.06
PVAS (Physician's Visual Analog Scale evaluation)	0.9 (−0.5, 2.3)	0.2	0.88 (−0.1, 1.8)	0.06
Inflammatory lesions	9.0 (2.7, 15)	0.01	7.56 (1.2, 14)	0.03

Table I

Topical azithromycin versus topical erythromycin in the treatment of acne vulgaris

	Lesion reductions in acne rosacea after treatment with azithromycin or erythromycin			
	Azithromycin (n=9)		Erythromycin (n=10)	
Lesions assessed	Mean (95% CI)	p	Mean (95% CI)	p
Papules	0.6 (−4.2, 5.3)	0.8	4.6 (0.5, 8.7)	0.03
Pustules	0.2 (−4.0, 4.4)	0.9	−0.2 (−3.3, 2.9)	0.9
Comedones	0.3 (−1.3, 2.0)	0.7	1.0 (−1.2, 3.2)	0.3
Nodules	0	0	−0.3 (−1.0, 0.4)	0.3
Total lesions	0.2 (−0.3, 5.2)	0.5	5.1 (0.5, 9.7)	0.03
PVAS (Physician's Visual Analog Scale evaluation)	0.2 (−0.3, 0.7)	0.4	0.4 (0.03, 0.8)	0.04
Inflammatory lesions	0.8 (−3.9, 5.5)	0.7	4.4 (1.1, 7.7)	0.01

Table II

Topical azithromycin versus topical erythromycin in the treatment of acne rosacea

was no significant reduction in these lesions with azithromycin treatment. Efficacy results combining acne vulgaris and rosacea subjects are presented in Table III.

Adverse events

Most acne subjects tolerated the topical applications without adverse events. Rosacea patients reported minor dryness, burning, and irritation upon initial applications. All adverse events were mild, and no subjects discontinued participation in the study due to adverse events.

Discussion

Antibiotics are generally recognized as effective treatments for acne vulgaris. Their effectiveness

	Lesion reductions in acne vulgaris and acne rosacea after treatment with azithromycin or erythromycin			
	Azithromycin (n=19)		Erythromycin (n=19)	
Lesions assessed	Mean (95% CI)	p	Mean (95% CI)	p
Papules	1.8 (−2.3, 5.9)	0.4	4.8 (2.4, 7.2)	0.0007
Pustules	3.3 (−0.4, 7.0)	0.1	1.1 (−1.3, 3.5)	0.4
Comedones	1.4 (−2.3, 5.1)	0.5	6.6 (−1.4, 14.6)	0.1
Nodules	0.05 (−0.2, 12.8)	0.6	−0.05 (−0.5, 0.4)	0.8
Total lesions	6.5 (0.2, 12.8)	0.06	12 (3.0, 21.0)	0.02
PVAS (Physician's Visual Analog Scale evaluation)	0.6 (−0.1, 1.3)	0.01	0.4 (0.2, 1.0)	0.007
Inflammatory lesions	5.1 (1.4, 8.8)	0.02	5.9 (3.0, 14.8)	0.001

Table III

The effectiveness of topical azithromycin versus topical erythromycin in the reduction of both acne vulgaris and acne rosacea lesions

may derive from their inhibition of bacterial growth such as *P. acnes*. Bacteria such as *P. acnes* have the ability to liberate free fatty acids from sebum. Lipases and free fatty acids are partly responsible for the formation of inflammatory lesions.[10] Several studies have established topical erythromycin as an effective acne treatment.[8,10] Azithromycin's pharmacokinetic profile suggests possible advantages for topical treatment.[12] This study was designed to determine whether azithromycin, a newer macrolide with a distinctive pharmacological profile, is effective in the topical treatment of acne vulgaris and/or rosacea by comparison with erythromycin treatment.

Results from phase I indicate that azithromycin is soluble in an ethanol and dH_2O solution without the need for propylene glycol. It also demonstrates that azithromycin prepared in 60% ethanol is essentially stable over the test period and should be sufficiently stable for drug delivery. Many factors affect pharmaceutical stability such as the stability of active ingredient(s), potential interaction between active and inactive ingredients, container/closure system, manufacturing process, and environmental conditions encountered during handling and storage.[14] Temporal stability can be defined as the time from manufacturing until the chemical activity of a compound is not less than a predetermined level, and its physical characteristics have not changed appreciably. A stable solution should remain clear over a relatively wide temperature range (4–47°C).[15] The stability assessment for solutions should also include a study of pH changes throughout its shelf life. This study demonstrates that azithromycin's solubility and stability is maintained in a 60% ethanol, pH 6.8 for 6 months. A limitation of this study is that we have not investigated in vitro penetration of the drug.

In phase II, using a known efficacious agent, we were able to tell if the study methodology was adequate to detect improvement in acne and rosacea. The primary outcomes for acne vulgaris and rosacea show the efficacy of erythromycin. These results indicate that, though small, this study does have the power to detect improvement in acne and rosacea. We found, for azithromycin treatment of acne, statistically significant improvement with inflammatory lesions but not with non-inflammatory lesions. This is expected given the efficacy of azithromycin treatment for inflammatory acne lesions.[12] This reduction may be attributed to azithromycin's superior uptake into phagocytes, which are a component of inflammatory lesions. This would suggest that for patients presenting this type of lesion, azithromycin may be a superior treatment to erythromycin. Our study was not powered, however, to detect statistical differences between the two drugs, and conclusions about relative efficacy of azithromycin and erythromycin requires confirmation in a larger trial.

Rosacea can be distinguished from acne vulgaris through the absence of comedones. This inflammatory disorder has an unknown etiology.[3] It is generally accepted that antibiotics are an effective means of controlling the papulopustules and erythema of rosacea.[3,11,16] The previously discussed pharmacokinetic profile of azithromycin offered reasonable belief that a topical formula would prove superior to other antibiotics in the reduction of rosacea lesions. There were no significant reductions in the number of rosacea lesions after azithromycin topical treatment ($p>0.05$). This suggests that azithromycin is not an effective treatment for rosacea.

While the small size of the exploratory trial is a limitation, we were able to detect statistically significant improvement with erythromycin in both acne and rosacea subjects. The target sample was projected to provide pilot information for magnitude of differences. Due to the pilot study nature of this trial we measured improvements but not intention-to-treat. The results suggest that erythromycin is superior to azithromycin in the treatment of rosacea and non-inflammatory lesions of acne vulgaris, but that azithromycin may have an advantage as a treatment for inflammatory acne lesions. Although a larger, placebo-controlled trial might show some efficacy for azithromycin in rosacea, the availability of other agents with greater efficacy suggests this is not worth exploring. Though it appears that the formulation of topical azithromycin was at least comparable with topical erythromycin, larger studies would be needed to determine whether topical azithromycin has any significant advantage over topical erythromycin.

References

1. Weiss JS. Current options for the topical treatment of acne vulgaris. *Pediatr Dermatol* (1997) **14**: 480–8.
2. Russell JR. Topical therapy for acne. *Am Fam Physician* (2000) **61**: 357–65.
3. Wilkin JK, Dewitt S. Treatment of rosacea. Topical clindamycin versus oral tetracycline. *Int J Dermatol* (1993) **32**: 65–7.
4. Weston WL, Morelli JG. Steroid rosacea in prepubertal children. *Arch Pediatr Adolesc Med* (2000) **154**: 62–4.
5. Eady EA, Cove JH. Topical antibiotic therapy: current status and future prospects. *Drugs Exp Clin Res* (1990) **16**: 423–33.
6. Fulton JE, Pablo G. Topical antibacterial therapy for acne. *Arch Dermatol* (1974) **110**: 83–6.

7. Toyoda M, Morohashi M, An overview of topical antibiotics for acne treatment. *Dermatology* (1998) **196**: 130–4.
8. Bernstein JE, Shalita AR, Topically applied erythromycin in inflammatory acne vulgaris. *J Am Acad Dermatol* (1980) **2**: 318–21.
9. Hellgren L, Vincent J, Topical erythromycin for acne vulgaris. *Dermatologica* (1980) **161**: 409–14.
10. Lesher JK, Chalker DK, Smith JG, et al, An evaluation of 2% erythromycin ointment in the topical therapy of acne vulgaris. *J Am Acad Dermatol* (1985) **12**: 526–31.
11. Mills OH, Kligman AM, Topically applied erythromycin in rosacea. *Arch Dermatol* (1976) **112**: 553–4 [Letter].
12. Fernandez-Obregon AC, Azithromycin for the treatment of acne. *Int J Dermatol* (2000) **39**: 45–50.
13. Fulton JE, Pablo G, Topical antibacterial therapy for acne. *Arch Dermatol* (1974) **110**: 83–6.
14. Code of Federal Regulations, Title 21 Food and Drugs, vol. 4. Food and Drug Administration, Department of Health and Human Services: Rockville, MD, 2001: Chapter I.
15. Vadas EB, Stability of pharmaceutical products. In: Gennaro AR, Chase GD, Mardersosian AD, et al, eds. *Remington's Pharmaceutical Sciences*, 18th edn. Mack Publishing Co: Easton, PA: 1990: 1504–12.
16. Hirshmann JV, Topical antibiotics in dermatology. *Arch Dermatol* (1988) **124**: 1691–700.

This document contains
COLOR figures/plates.

Best available copy.